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Implementing treatment of opioid use disorder in rural settings: A focus on HIV and Hepatitis C prevention and treatment

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Abstract

Purpose of review: To describe the epidemiology opioid use disorder in the rural United States as it pertains to HIV and hepatitis C transmission and treatment resources.

Recent findings: Heroin and fentanyl analogues have surpassed prescription opioids in their availability in rural opioid markets adding to HIV and hepatitis C (HCV) and overdose risks. Only 18% of rural individuals live in towns with inpatient services which are of limited quality and utility. Opioid treatment programs that provide methadone are not located in rural areas and only 3% of the primary care providers have the ability to prescribe buprenorphine. National models and resources have been established but lack implementation in rural areas leading to ongoing HIV and HCV transmission and overdose.

Summary: Addressing the adverse impact of opioids in the rural U.S. will require a concerted effort to implement effective treatments according to national standards.

Introduction

The rise in prevalence of opioid use disorder (OUD) presents unique challenges in rural parts of the United States (U.S.). The link between OUD, HIV and hepatitis C (HCV) transmission risk, from both sexual and injection routes, creates additional imperatives to address these challenges to ensure an effective response that minimizes morbidity, mortality and improves public health. The purpose of this review is to describe the epidemiology of opioid use in the rural U.S., especially as it pertains to HIV and HCV transmission, highlight the evidence-based options for treatment of OUD, describe how effective treatment for OUD can reduce the additional harms associated with opioid use (HIV/HCV), and discuss barriers

to care, future research directions and the policy implications for increasing treatment of OUD for rural people.

Epidemiology of Rural Opioid Epidemic

We are now almost two decades into the prescription opioid epidemic in the U.S. [1, 2]. The earliest reports of prescription opioid misuse were largely from rural areas, and rural Appalachia in particular. The first inklings of this issue were published as case reports; patients were seeking treatment for OUD where the opioid of choice was OxyContin® [3, 4]. This was followed by larger-scale epidemiologic studies in predominantly rural areas [5–8], demonstrating widespread misuse of prescription opioids. More recently, heroin and fentanyl have surpassed prescription opioids in their availability on the illicit market and now commonly used among those previously misusing prescription opioids [9–11], leading to a significant increase in fatal overdose rates [12, 13]. Perhaps most surprising in the early studies of prescription opioids were reports of frequent injection of these drugs [5, 14]. Injection of prescription opioids, and more recently heroin, is driving the concurrent hepatitis C (HCV) epidemic in young people who use drugs [15–18] and led to an outbreak of HIV in rural Indiana [19, 20]. Further, the impact of the prescription drug epidemic on rural areas has not waned; a recent hotspot analysis identified U.S. counties at high risk for HIV and HCV stemming from opioids, and the vast majority were in rural Appalachia [21].

HCV, until recently, was viewed among physicians as a chronic disease largely afflicting Baby Boomers [22]. However, a rapidly changing demographic has been observed of late, whereby young people who use drugs, and those who inject opioids in particular, are driving an increase in new HCV infections [15–17]. The epidemic curve has also shifted dramatically, where the peak in 2002 was squarely among Baby Boomers. Within seven years, however, a bimodal distribution was observed, with peaks in both Baby Boomers as well as younger drug users age 18–24 [22]. Zibbell and colleagues posit that people who inject prescription opioids are at particular risk for HCV [16], as well as HIV [19]. According to Zibbell, the way in which prescription drugs are prepared for injection, as well as the high cost of some prescription opioids escalates splitting/sharing behaviors (this played a key role in the HIV outbreak in Indiana), thereby increasing the risk for HCV and HIV transmission [16, 19]. Without treatment for HCV, the potential is also great for increasing rates of sequelae of chronic liver disease and hepatocellular carcinoma [23]. However, direct-acting antiviral drugs (DAAs) represent a vast improvement on earlier treatment regimens and offer cure rates upwards of 100% [24]. The current barriers to treatment for HCV with DAAs are primarily around cost and access [25], especially among people who use drugs [26].

Rates of HIV have been declining in the United States [27]. However, in 2015 an outbreak was reported in Scott County, Indiana, a rural area just north of Louisville, Kentucky [20]. A total of 181 cases was reported, primarily among people who inject drugs (PWID) reporting injection of oxymorphone (Opana® brand, specifically), an extended-release, prescription opioid. Extensive case investigations identified dense networks of PWID in Scott County that facilitated the rapid spread of HIV through the drug using community and their sex partners [20]. These drug networks resemble those found in other rural areas [28], prompting

concern for those in other rural communities at risk for similar outbreaks [21]. The response to the outbreak included implementation of various harm reductions strategies, including syringe exchange, HIV/HCV screening and access to medication-based treatment for opioid use disorders [29].

As injection of opioids (both heroin and prescription) in rural areas continues, the need for evidence-based treatments to address OUD cannot be understated. Increased access to medication-based treatment is clearly indicated, as the options (methadone, buprenorphine, and naltrexone) have all been demonstrated to be effective in treating OUD and reducing associated harms.

Treatment availability in rural areas

Rural areas present a number of challenges to the provision of effective treatment of OUD. Some of these barriers add to the usual barriers such as stigma, incorrect understanding of the role of partial and full opioid agonists in the treatment of OUD, limited access to medication-based treatments, limited supply of appropriately trained treatment providers, and others, seen in larger metropolitan regions of the country. Uniquely, the relatively low population density of rural regions exacerbates the challenges seen elsewhere. These challenges are seen across the spectrum of treatments including inpatient and outpatient settings.

Inpatient settings

Inpatient treatment of OUD disorder is indicated when outpatient strategies have failed. However, most of the effective medication treatments for OUD are not allowed or provided in inpatient treatment settings (e.g., residential treatment). Therefore, the frequent misconception that treatment for OUD needs to start with an inpatient admission and the call for more “beds” to address the opioid epidemic likely shunts patients away from effective treatments [30]. Inpatient treatment includes a variety of strategies typically adapted from older models that were developed to initiate treatment of alcohol use disorder [31]. These include the management of opioid abstinence or withdrawal with medications to address symptoms such as arthralgias, myalgias, nausea, diarrhea, anxiety, insomnia and autonomic signs such as elevated blood pressure. These “detoxifications” do not address the underlying neurobiology of OUD, are of limited efficacy and leave the patient with a lowered opioid physical tolerance and increased risk for opioid overdose. Brief opioid withdrawal management may be coupled with additional psychosocial services and extended inpatient (e.g. residential) or partial inpatient management. Relapse to opioids is common following inpatient and residential treatments. Patients who leave brief or extended inpatient treatments typically have lowered levels of opioid tolerance and are therefore at increased risk of fatal and non-fatal overdose after leaving inpatient settings. Finally, the relatively brief nature of detoxification and residential treatments do not allow for an ongoing focus on infectious complications associated with OUD, such as HIV or HCV transmission.

A national survey of rural “detoxification” services revealed that only 18% of rural residents live in a town with these services [32]. Rural facilities that provide these services rarely: (1) offer the range of treatments endorsed by national medical societies such as the American

Society of Addiction Medicine, (2) have services tailored for populations such as adolescents, elderly, or women, (3) accept public insurance or use sliding fee scales, (4) provide prompt admission, or (5) link patients to robust addiction treatment services on discharge [32]. Thus, given limited efficacy, availability and services, rural inpatient treatment of OUD is unlikely to have a substantial impact for the vast majority of individuals with OUD; however, expansion may be critical to address the needs of individuals who do not derive benefit from outpatient treatment or to help with the initiation of naltrexone (see below).

Outpatient settings

Medication-based treatments—As indicated above, the most effective treatments for OUD are typically provided through outpatient settings. Treating OUD decreases risky injection and sexual HIV transmission risk behaviors as well as opioid use and overdose [33, 34]. The National Institute of Health indicates that medications are the standard of care for treating OUD and decreasing HIV transmission among people who use drugs [35]. There are three medications that are approved by the Food and Drug Administration (FDA) for the treatment of OUD. Methadone, a full mu agonist may be legally delivered only in federally-licensed outpatient clinics in the U.S. (i.e., opioid treatment program or OTP).

Buprenorphine, a partial mu opioid agonist typically co-administered with naloxone in roughly a 4:1 ratio, may be delivered in office-based practices by specially providers who have completed training according to the Drug Addiction Treatment Act of 2000 (DATA 2000) [36]. Naltrexone, an opioid antagonist, can be administered in any setting and requires no specialized licensure or training. Methadone and buprenorphine have the best evidence regarding their effectiveness in decreasing HIV risk behaviors and transmission [37]. All three medications can be used to treat OUD in patients with HIV infection. Methadone, because of complexities in its metabolism and pharmacokinetics, may be more prone to clinically meaningful drug-drug interactions when given with antiretrovirals (ART) compared to buprenorphine or naltrexone, but can be readily managed with monitoring.

Buprenorphine and methadone are both effective in decreasing opioid use and overdose-and all-cause mortality among people with opioid use disorder [38]. Buprenorphine delivered in a primary care setting decreased HIV transmission risk behaviors among HIV uninfected patients in one single center, observational study [34] and among HIV transmission risk among HIV-positive patients with OUD when provided in HIV clinics [39]. A meta-analysis of 12 studies examining the impact of opioid agonist therapy (methadone or buprenorphine) on HIV transmission estimated that opioid agonist therapy decreases new HIV infections by 54% (rate ratio 0.45; 95% CI 0.32, 0.67)[40]. Likewise, treating HIV-infected persons for HIV decreases HIV viral load—the main host determinant of HIV transmission—and decreases transmission apart from change in risk behavior [41]. In one study conducted in Vancouver, British Columbia, combining ART and opioid agonist treatment for people who inject drugs decreased new HIV infections both among PWID and in the community overall [42, 43].

Naltrexone is an opioid antagonist available originally as a daily oral formulation that, while pharmacologically efficacious, was not effective due to difficulty initiating treatment (i.e., a

sustained period of opioid abstinence is required to avoid naltrexone-induced precipitated withdrawal), poor patient adherence and high drop-out rates. An injectable extended-release formulation that lasts 28 days is marketed that was intended to obviate problematic adherence. A recent study demonstrated that, among the subset of patients who were able to initiate extended-release naltrexone, there were comparable reductions in opioid use compared with buprenorphine; however, a significant number of patients were not able to initiate naltrexone therapy [44]. There is also a concern that individuals may be at greater risk for overdose due to decreased opioid tolerance when they discontinue treatment with naltrexone. Nonetheless, naltrexone can be efficacious in the certain patient populations. One randomized trial of extended-release naltrexone versus placebo in Russia (where agonist therapy is illegal) included 40% with HIV infection and 88% with hepatitis C infection and found no difference in serious adverse event or liver injury in patients with and without HIV or HCV infection [45, 46]. A pilot study of extended-release naltrexone versus treatment as usual for opioid and/or alcohol use disorder demonstrated safety and feasibility of use in outpatient HIV clinics [47]. The National Institute of Drug Abuse Clinical Trials Network CTN-0067 CHOICES multi-site clinical trial is currently underway to assess effectiveness in U.S. HIV clinics for people with HIV and OUD.

Supply and access to effective outpatient treatments in rural settings

A recent review from the Agency for Healthcare Research and Quality (AHRQ) outlines many of the factors involved in the provision of medication treatment for OUD in rural settings [48]. The review highlights the role of barriers such as workforce, stigma, relapse prevention services, logistical barriers for practices such as time constraints, and costs. Despite the over 1000 OTPs with the ability to provide methadone in the U.S., few are situated in rural settings. Therefore, most research conducted on the availability of medication treatment in rural settings has focused on buprenorphine.

Since the passage of the DATA 2000 [36] allowing for the provision of office-based treatment of OUD, the provision of buprenorphine has increased in rural settings. A study of national Drug Enforcement Administration (DEA) data on medication distribution demonstrated that there was an increase in the number of grams of buprenorphine dispensed in rural areas between the years 2004 to 2011 [49]. Some of this coincided with the increase in the number of patients who could simultaneously receive prescriptions from a single physician from 30 to 100 that was enacted in 2006. This care is typically provided by primary care providers. For instance, a 2011 survey of rural prescribers in Washington state demonstrated that the large majority (52–89% across large, small and isolated rural areas) were trained in Family Medicine [50]. Safety net providers (e.g. Federally Qualified Health Centers [FQHC], Rural Health Centers) accounted for the vast majority of providers across these rural settings. Importantly, however, a 2012 national study demonstrated that only 3.0% of primary care physicians, the group providing the majority of health care in rural settings, have the ability to prescribe buprenorphine [51]. Most rural areas have no prescribers with a DEA registration (i.e. waiver) allowing them to prescribe buprenorphine under DATA 2000. Recent changes to the law allowing for buprenorphine prescribing by advanced practice professionals, such as nurse practitioners and physicians assistants, may help to address this disparity.

Models of care for medication treatments

A narrative review identified models for integrating treatment of opioid use disorder in primary care [52]. Several of these primary care-based models, including office-based opioid treatment, nurse-facilitated treatment, Project Extension for Community Healthcare Outcomes (ECHO), “hub and spoke” and “one-stop shop” are particularly salient for use in rural areas where substance use disorder treatment services are limited.

Office-Based Opioid Treatment (OBOT)

In the office-based opioid treatment (OBOT) model, physicians, nurse practitioners and physician assistants (depending upon state law) may receive a DATA 2000 waiver to prescribe buprenorphine for the treatment of OUD in outpatient medical care settings after completing required treatment. Often, a clinic staff person (typically a nurse, counselor, or medical assistant) coordinates care for patients receiving buprenorphine, facilitating regularly scheduled visits, urine toxicology testing, and prior authorization requests, and works collaboratively with the clinician [53–55]. Psychosocial services include regular brief counseling provided by the physician, other clinic staff; other referral for off-site counseling.

The Buprenorphine HIV Evaluation and Support (BHIVES) collaborative model used the OBOT framework to develop a chronic care model that integrates buprenorphine treatment with HIV primary care [56–66]. Like the OBOT Model, a clinic coordinator collaborates with a prescriber to provide buprenorphine. Patients receive buprenorphine in the context of HIV treatment, often prescribed by the same primary care provider. A Health Resources Service Administration [67] monograph promotes adoption of BHIVES in US HIV clinics, and BHIVES is considered the standard of care for engaging HIV-infected patients with OUD in treatment [68, 69].

Nurse Care Manager Model

Nurse care managers have been used to increase capacity for OBOT in Massachusetts FQHCs, where Massachusetts Medicaid reimburses nurses for OUD care management [70–72]. In this model, nurse care managers collaborate with primary care prescribers to provide buprenorphine and, to a lesser degree, extended-release naltrexone. Community healthcare center prescribers are supported with DATA 2000 training. The nurse care manager performs initial intake visits and education, as well as ongoing coordination of OUD treatment and other medical issues, including coordination of prior authorization requests, communication with pharmacists, and perioperative care coordination, freeing prescribers to manage more patients. When implemented in 19 community healthcare centers in Massachusetts, the number of DATA 2000 waived physicians increased 375% and the number of new OBOT patients enrolled per year increased from 178 in 2007 to 1210 in 2012 [72]. Many states have Ryan White Care Act-funded HIV nurse care managers that serve clients in rural regions, creating potential for a combined nurse care manager model to improve access to care for both HIV and OUD in the rural U.S.

Project Extension for Community Healthcare Outcomes (ECHO)

Project Extension for Community Healthcare Outcomes (ECHO) links primary care providers with inter-disciplinary expert consultation and training through an Internet-based audiovisual network [73] and has been adapted to support rural primary care providers in buprenorphine treatment of OUD [74]. It may be considered a rural adaptation of the hub and spoke model (see below) with “hub” centers linked via weekly educational conferences to rural primary care “hubs.” A typical one-hour, weekly ECHO curriculum consists of a brief (15 minute) didactic followed by primary care provider presentation of recent cases and feedback discussion from an expert panel composed of physicians, behavioral health counselor, and sometime a peer with lived experience of their own substance use disorder. There is also an emphasis on recruitment of physicians for buprenorphine waiver training and provision of continuing medical education in OUD. This model is well-suited for enhancing rural primary care provider capacity to treat patients with OUD. Implementation of an ECHO model to support buprenorphine prescribing was associated with a marked increase in DATA 2000-waiver buprenorphine prescribers in rural New Mexico [74]. Similarly, ECHO demonstrations have been used to support HCV [75–78] and HIV [79] treatment among rural primary care providers.

Hub-and-Spoke Model for OUD

In response to the inadequate treatment access despite successfully increasing the number of potential buprenorphine providers, Vermont developed and implemented a model of care called the “Hub and Spoke” [80], a model used previously for the treatment of chronic and often complex diseases. A “hub” is a specialized expert center (in this case, there were 5 regional hubs identified to provide statewide coverage) that are able to assist regional providers (the “spokes”) by providing expert care advice and also allowing for seamless transfer of patients from community providers back and forth between the hub and spoke as needed (e.g., for restabilization, induction or re-induction, complex associated medical issues). The spoke providers could practice in an array of settings (e.g., private practice, FQHC) as the aim was to provide support to community providers in order to expand provision and enhance quality of care. In addition, teams were developed that were comprised generally of a nurse and behavioral health specialist that support the clinicians by conducting patient intakes/assessments and then manages many other ongoing treatment activities (e.g., delivers counseling, arranges for urine toxicology testing). Finally, a centralized learning collaborative has been developed that offers ongoing training on evidence-based practices [81]. The opportunity to develop and sustain this model of care is the result of forward-thinking state legislation working closely with clinical experts along with a favorable insurance/Medicaid landscape in Vermont.

Crisis Intervention: The One Stop Shop Model

The 2015 outbreak of 181 newly diagnosed HIV infections (with 92% hepatitis C co-infection) in rural Scott County, Indiana was associated with injection of extended-release oxycodone [82, 83]. In the absence of trained treatment providers, local public health officials along with experts dispatched to the region by the Centers for Disease Control and Prevention and the Substance Abuse and Mental Health Services Administration

(SAMHSA) an integrated care model was established in the town's existing mental health clinic (LifeSpring Health Systems) to provide HIV and HCV treatment, OUD treatment with extended-release naltrexone and buprenorphine mental health services, and primary care. An emergency syringe exchange program and HIV screening services were implemented in the community with beneficial results [29]. Peer navigators and social workers provide coordination with primary care providers. This model was implemented with considerable state and federal support in the context of the outbreak, but offers an ideal framework for community-based, integrated treatment and prevention of HIV and HCV, mental health disorders, and OUD. Integrated local, state, and federal funding models will be required to sustain such responses. Similar models might be appropriate for rural communities with high prevalence of injection drug use to stem the potential for HIV and HCV transmission.

The potential role of novel medication formulations in rural areas

There are novel sustained-release formulations of buprenorphine either now marketed or under review by the Food and Drug Administration (FDA) that could improve access to care in rural areas as they may decrease the required frequency of in-person clinic visits for stable patients and may assist with concerns regarding diversion. There is a 6-month subdermal implant that used similar technology to implantable birth control (brand name Probuphine®) [84]. The implant requires a physician trained and qualified to do the minor implant procedure and licensed to prescribe buprenorphine. The implant produces lower plasma concentrations of buprenorphine and is intended for patients already stable on 8 mg/day. In 2017 a novel sustained release subcutaneous formulation of buprenorphine (brand name Sublocade®)[85] that provides one-month controlled exposure to buprenorphine comparable to 24 mg/day was approved and should be available for use soon. A second subcutaneous formulation that offers both weekly and monthly coverage over a range of doses is currently under review by the FDA [86]. These novel formulations may offer more flexibility to clinicians and patients and may have an important role in expanding access to treatment in rural areas when integrated into some of the models of care described previously. Funding models for extended-release preparations remains challenging, with subcutaneous buprenorphine retailing at \$1500 per injection and probuphine retailing at \$4,950 for a 6-month implant.

Policy and research agenda moving forward

Appropriate policy responses to the untreated OUD in rural settings must address the large numbers of rural individuals who don't have access to the most effective treatments. National stakeholder agencies have created documents that can help states and local counties that are interested in ensuring that their constituents have access to the most effective treatments (e.g., National Rural Health Association, National Governor's Association, National Academy for State Health Policy, AHRQ). Key to these efforts is a need to review and remove regulatory and funding barriers that hamper the expansion of medication-based treatments. In addition, several models of care and support provide templates that can be deployed in rural areas to address training and workforce constraints in the primary care practices that provide most health care in rural settings. These include the hub and spoke model, Project ECHO, the SAMHSA funded-Prescribers Clinical Support System for

Medication Assisted Treatment and the nurse care manager models. The Bureau of Primary Care in the Health Resources Service Administration can assist in implementing such programs through its support of federally qualified health centers and rural health centers. Similarly, newer extended release formulations of buprenorphine and naltrexone, and aspects of telehealth/telemedicine, provide unique opportunities for the challenges of distance and visit frequency in rural areas.

Many of the challenges to the provision of effective treatment of OUD in rural areas pertain to implementation. Therefore, future research should include an emphasis on the use of methods from Implementation Science that focus on addressing barriers to uptake of effective treatments. Standard outcomes for this type of research include treatment feasibility, acceptability, adoption, fidelity, cost, sustainability and penetration. In addition, hybrid effectiveness/implementation research designs allow for the simultaneous collection of treatment and implementation outcomes. Rural regions and providers have not traditionally been involved in the treatment of OUD and so substantial emphasis will need to be paid to issues of patient, provider and community acceptability and treatment retention. In addition to increasing access to care, attention to issues of quality and fidelity will be needed to ensure appropriate implementation and minimize poor outcomes, such as medication diversion. Newer extended-release formulations may help address these concerns as well.

Conclusions

Certain treatments for OUD are effective in decreasing morbidity, mortality, HIV and HCV transmission. The best evidence supports the use of partial and full agonist treatments (buprenorphine and methadone). Other treatments are often ineffective in treating OUD (detoxification) or may decrease illicit opioid use but have not yet been shown to decrease HIV or HIV transmission (extended-release naltrexone). Methadone, buprenorphine or naltrexone can all be used in most patients with HIV and/or HCV. National models and resources exist to support the implementation of such treatment but deployment has been limited leading to ongoing adverse impacts. Rural providers who have successfully incorporated the care of OUD into their practice can serve as models for implementation for the foreseeable future.

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